Summary of RotaTeq™ Vaccine Reports to VAERS, 3/1/06-2/15/07

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Outline

- Reports to the Vaccine Adverse Event Reporting system (VAERS)
- Update:
  - Vaccine Safety Datalink (VSD) study
  - Merck phase 4 study
- Data interpretation

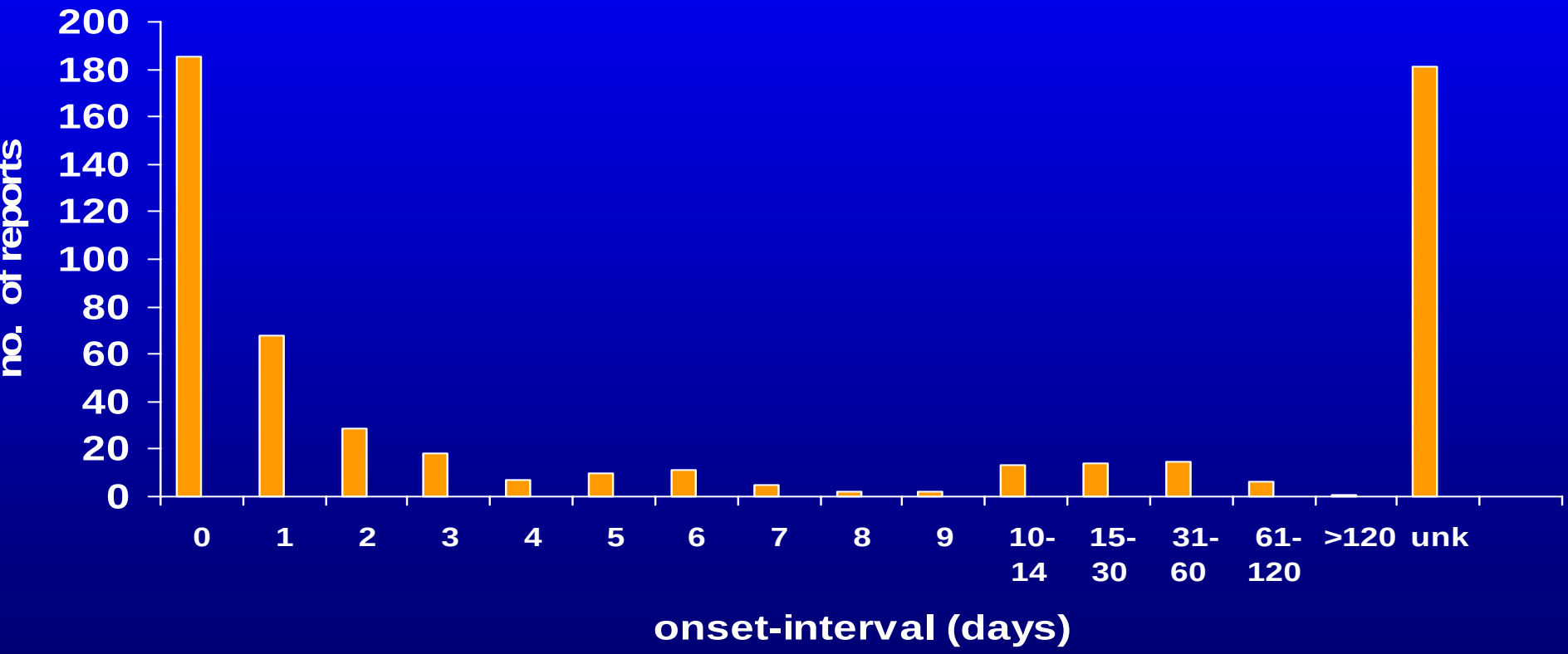
VAERS RotaTeq™ reports

- **3.6 million doses distributed (March 2006- January 31, 2007)***

- **From March 1st, 2006 – February 15, 2007 VAERS received total of 567 reports following vaccination**
  - **RotaTeq alone: 291 (51%)**
  - **1st dose: 322 (57%)**
  - **Most frequently reported adverse events: Diarrhea (27%) and vomiting (26.5%)**

*** Merck personal communication**

RotaTeq™ Reports by Onset-Interval (days) (N=567)

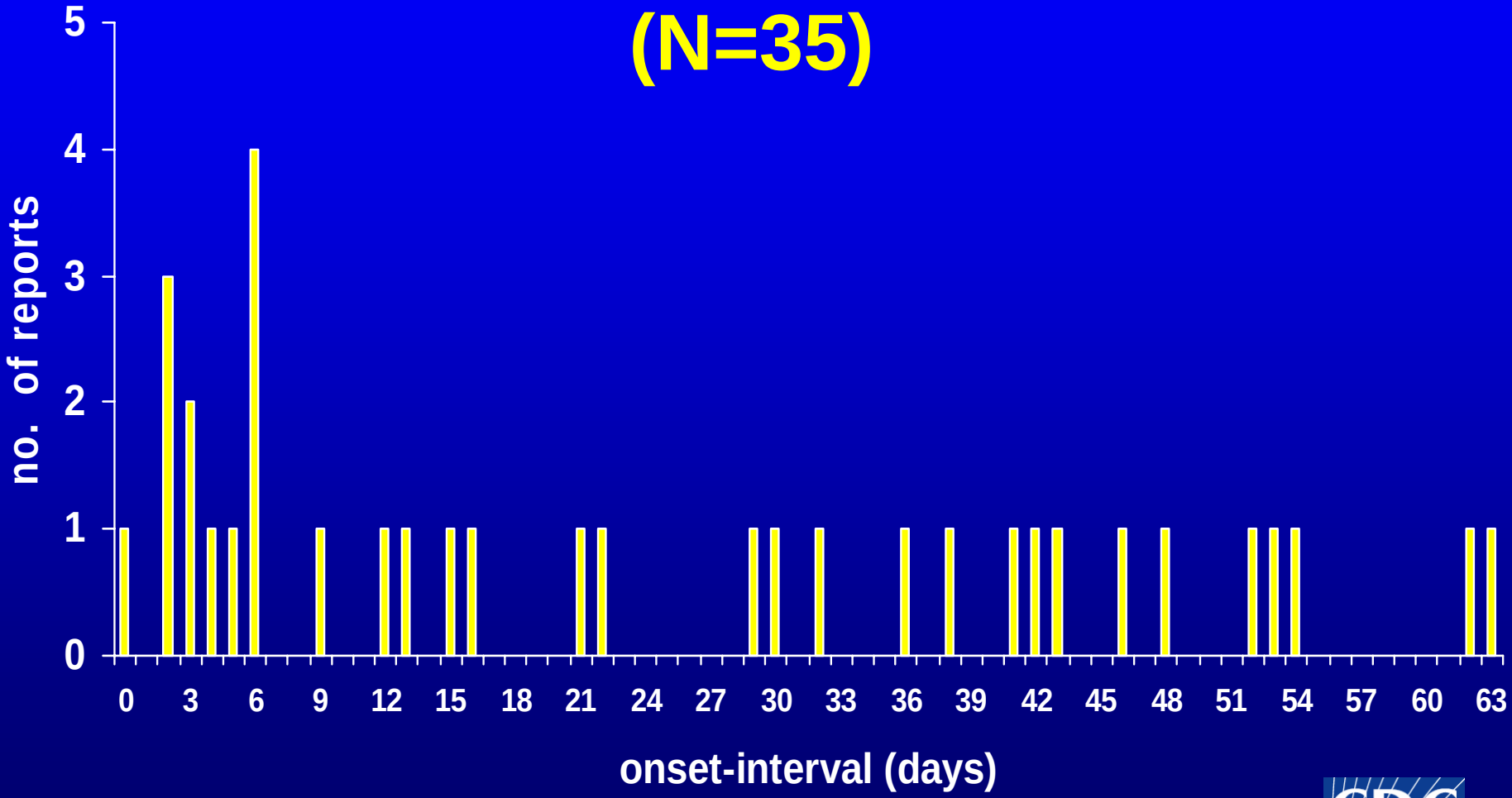


Reports as of February 15, 2007; 50% of reports 0-2 days post vaccination;
32% onset date was not reported

Summary of Intussusceptions (IS) Reported to VAERS

- 35 IS confirmed reports through 2/15/07
  - 17 reports 1-21 days
  - 11 of 17 were within 1-7 days
- No death reports

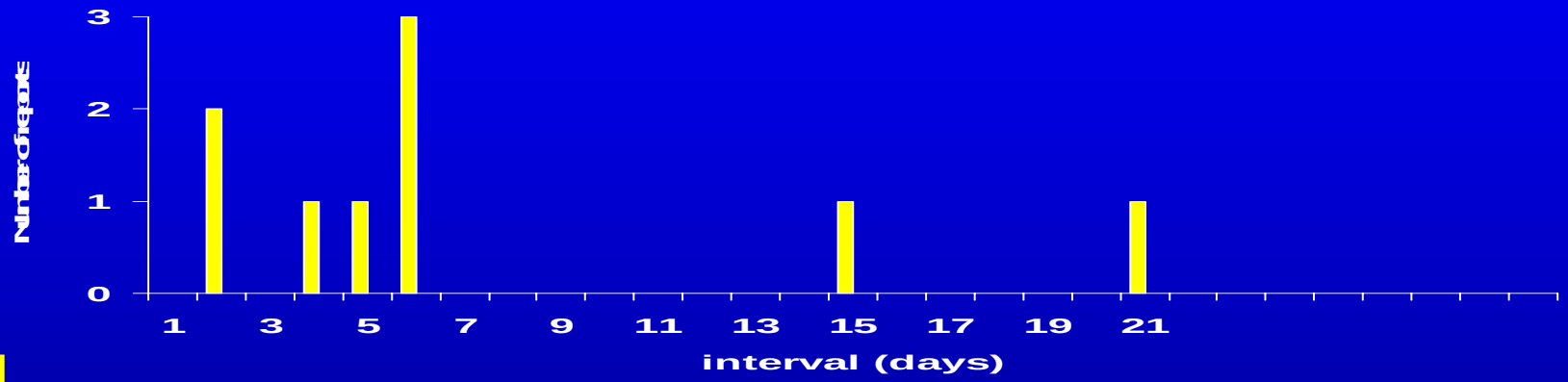
IS Reports by Onset-Interval—days after vaccination (N=35)



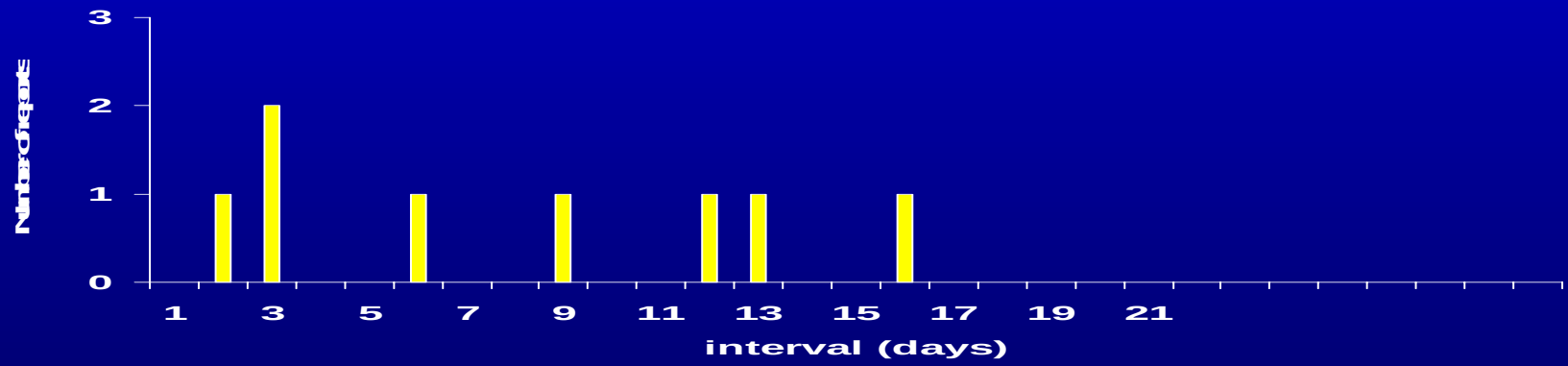
Reports as of February 15, 2007;

Intussusception Reports: Onset interval (1-21 days)

Dose 1
n = 9



Dose 2
n = 8



* **Dose 2: 1 report on day of vaccination**

Descriptive Epi of IS reports

- Mean (median) age at symptom onset was 17 (21) weeks
  - Range 10-37 weeks
- 43% Male; 46% Female; 11% gender not reported
- 12 (34%) had surgical reduction
- 8 (23%) surgical resection
- 13 (34%) contrast enema reduction
- 2 (6%)spontaneous resolution
- Lab results:
  - Tissue samples: 4 tested, none positive for rotavirus/ adenovirus
  - Stool samples: 2 tested, one tested positive for vaccine strain at day 6
    - expected after Rotateq administration

VSD RotaTeq™ Administration, February 14, 2007

- As of February 14, 2007, 28,377 RotaTeq vaccinations
  - 6 out of 8 sites participate in the study

- No Intussuception report within 30 days following RotaTeq vaccination

VSD RotaTeq™ Administration*, February 14, 2007

Age Group	Dose 1	Dose 2	Dose 3	Total
0-6 Weeks	9	0	0	9
6-14 Weeks	16,166	72	0	16,238
15-23 Weeks	728	8,009	10	8,747
24-35 Weeks	249	498	2,556	3,303
36-52 Weeks	18	6	6	30
NA	49	1	0	50
Total	17,219(61%)	8,586(30%)	2,572(9%)	28,377

*Data from 6 sites

Merck RotaTeq™ Post-licensure Safety Study*

- Prospective observational active surveillance
- Study population: in large insured population in US
  - Annual birth cohort ~100,000
  - Planned study size: 44,000 vaccinated children
- Study plan: Monitor rates of IS and overall vaccine safety
  - Compare rates to several control groups
  - 30 days post vaccination for each dose
- Update: 1,354 RotaTeq™ recipients through 2nd quarter 2006
    - Follow-up through Sep 30, 2006
    - No cases of intussusception
  - >16,000 1st dose vaccinees through Dec 2006

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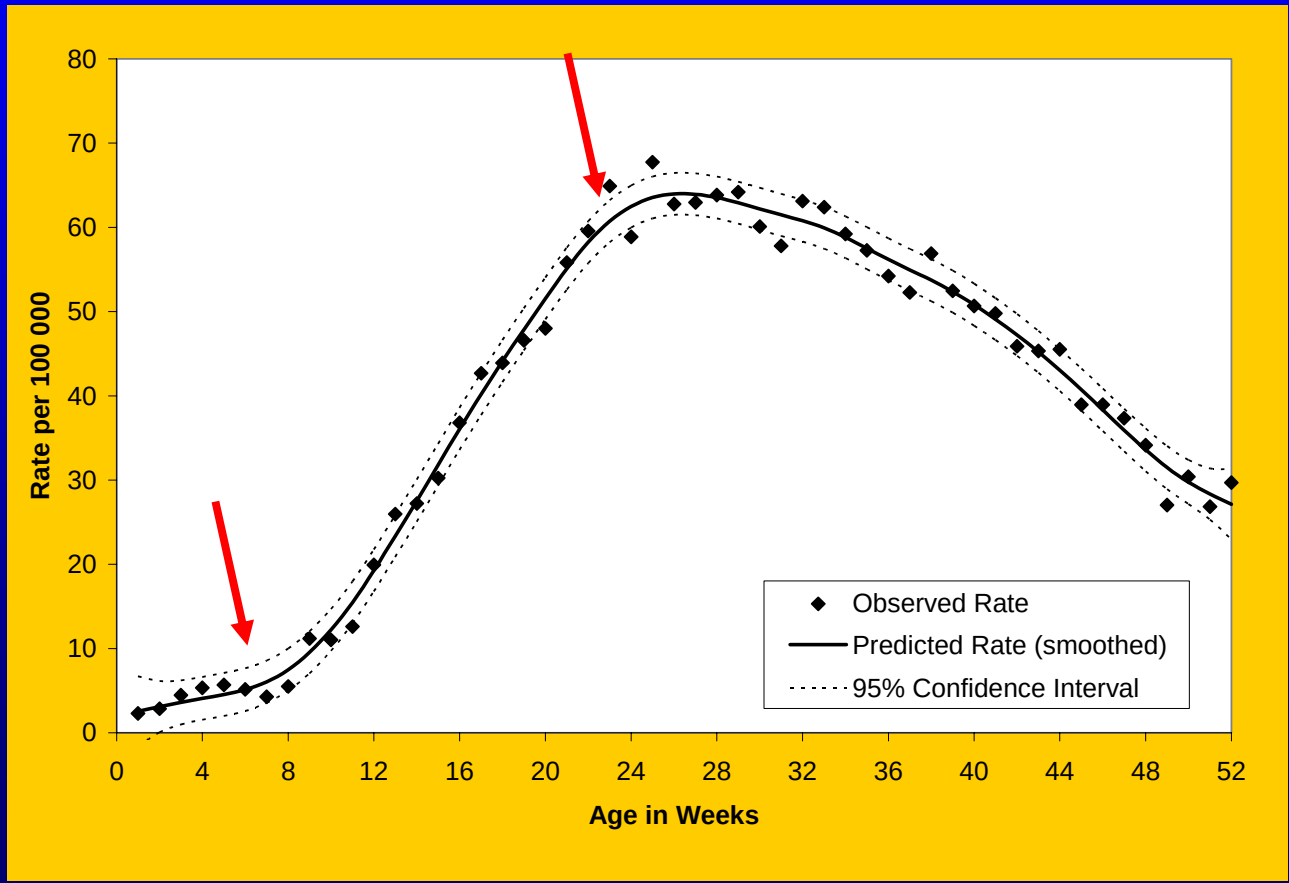
*source: Merck unpublished data , 2/16/07

Data Interpretation

Do the Observed Number of Intussusception Cases Exceed Expected?

- Observed:
  - VAERS cases
- Expected:
  - Baseline intussusception rate (age-stratified)
  - Number of vaccine doses administered (age-stratified)

Background Intussusception Rates by Week of Age 1993-2004



** Source: Tate et al. unpublished data using Healthcare Utilization Project (HCUP) database*

Background Intussusception Rates: 2000—2004

Onset age	VSD rate per 100 000 infants annually	HCUP rate per 100 000 infants annually*
6-14 weeks	18.1	12.5
15-23 weeks	32.5	43.7
24-35 weeks	42.5	58.1
TOTAL	**32.4**	**37.6**

**HCUP—Healthcare Cost and Utilization Project, National Estimates for 2000-2004*

Distribution & Age of Administration

- 3.6 million doses distributed* (through end of January 2007)

Age	**Proportion doses administered--VSD**
6-14 weeks	57%
15-23 weeks	31%
24-35 weeks	12%

*** Source: Merck, personal communication***

Summary: VAERS intussusception reports

- Time windows after vaccination
  - 1-21 days and 1-7 days after vaccination
  - Rotashield experience
  - Biological plausibility
- 35 confirmed reports after vaccination
- 17 cases within 1-21 days of RotaTeq
  - 11 of 17 cases were within 1-7 days

VAERS: Intussusception onset age

1-21 days after vaccination

Onset age	**Total IS cases**
6-14 weeks	7
15-23 weeks	9
24-35 weeks	1
TOTAL	**17**

1-7 days after vaccination

Onset age	**Total IS cases**
6-14 weeks	5
15-23 weeks	6
24-35 weeks	0
TOTAL	**11**

Observed versus Expected 1 to 21 Days*

Age Group	VAERS Cases	Expected Cases*
6-14	7	21
15-23	9	21
24-35	1	10
Total	**17**	**52**

Exact Poisson—Stratified by age group

Rate Ratio	Lower	Upper	P-Value
0.32	0.17	0.55	<0.0001

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** Source: VSD for background and age of vaccine administration; Merck distribution data*

Observed versus Expected 1 to 7 Days*

Age Group	VAERS Cases	Expected Cases*
6-14	5	7
15-23	6	7
24-35	0	3
Total	**11**	**17**

Exact Poisson—Stratified by age group

Rate Ratio	Lower	Upper	P-Value
0.61	0.29	1.18	0.153

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** Source: VSD for background and age of vaccine administration; Merck distribution data*

Data Assumptions

- Background intussusception rates
- VAERS reporting completeness
- Doses of vaccine administered and age of administration

Background Intussusception Rates

- Baseline IS rates vary by database
  - HMOs (VSD) versus national
- Completeness and accuracy of the ICD coding for inpatient databases
  - short-stay and emergency department (ED) discharges may not be captured
  - one study* suggests ~40% may be ED or short-stay

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** Source: Staat MA et al. Pediatr Res 2000; 49:242A*

VAERS Reporting Completeness

- Suspected to be high
- Awareness among providers after Rotashield experience
- RotaTeq
  - half of reported IS cases to VAERS > 21 days post-vaccination

Data Assumptions: Vaccine administration

- Vaccine distribution
  - 3.6 million doses* (through end January 2007)
  - Lag-time in administration
- Age at administration
  - RotaTeq vaccinations in VSD
  - RotaTeq vaccinations in US immunization registries

* *Source: Merck, personal communication*

Summary

- Observed intussusception rates are not greater than expected
- CDC continues to support the ACIP recommendation for routine immunization of all U.S. infants with three doses of RotaTeq
- Ongoing monitoring and recalculation of estimates

Acknowledgement

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